EXHIBIT B

FIFTEENTH EDITION

THE MERCK MANUAL

OF

DIAGNOSIS AND THERAPY

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FOREWORD

THE MERCK MANUAL first appeared in 1899 as a slender 262-page text titled MERCK'S MANUAL OF THE MATERIA MEDICA. It was expressly designed to meet the needs of general practitioners in selecting medications, noting that "memory is treacherous" and even the most thoroughly informed physician needs a reminder "to make him at once master of the situation and enable him to prescribe exactly what his judgment tells him is needed for the occasion." It was well received and, by the 6th Edition (1934), THE MERCK MANUAL had become highly valued by medical students and house staff also; by the end of World War II the pocket-sized manual was an established favorite ready-reference. Today THE MANUAL is the most widely used medical text in the world. While the book has grown to about 2500 pages, its primary purpose remains the same—to provide useful information to practicing physicians, medical students, interns, residents, and other health professionals.

Fewer physicians now attempt to manage the whole range of medical disorders that can occur in infants, children, and adults, but those who do must have available a broad spectrum of current and accurate information. The specialist requires precise information about subjects outside his area of expertise. All physicians need more and more information for study and examination purposes as well as for patient care. THE MERCK MANUAL continues to try to meet these needs, excluding only details of surgical procedures.

Precisely how do we attempt to meet these needs? First, from a disease orientation, THE MANUAL covers all but the most obscure disorders of mankind, not only those that a general internist might expect to encounter, but also problems of pregnancy and delivery, the more common and serious disorders of neonates, infants, and children, and many special situations. Disorders are mainly organized according to the organ systems primarily affected, on the basis of their etiology (as with most of the infectious diseases and disorders due to physical agents), or on the basis of disciplines (eg, gynecology, obstetrics, pediatrics, genetics, psychiatry). In addition, THE MANUAL contains information for special circumstances, such as radiation reactions and injuries, problems encountered in deep-sea diving, or dental emergencies. The entire book is updated for each new edition, and new subjects continue to be added, such as discussions of diagnostic and therapeutic procedures in gastroenterology, acquired immunodeficiency syndrome (AIDS), reproductive endocrinology, oncology, the management of severe and chronic pain, the value of hyperbaric O_2 therapy, and special considerations in drug treatment of infants and children. This edition has 114 pages (approximately 5%) more text than the preceding edition. We therefore urge you to check the Index whenever you require information, even on unusual subjects or those not commonly found in other texts.

A completely disease-oriented compendium, however, would have serious limitations. Since patients usually present with complaints or concerns that must be meticulously described, sorted, and deciphered, many chapters are devoted to discussions of symptoms and signs and how to elicit the historical and physical data required for diagnosis. Common clinical procedures and laboratory tests used as diagnostic and management aids are described with emphasis on their indications, contraindications, and possible complications. New and sophisticated laboratory and technologic procedures are also described, with comments on their uses, interpretations, and limitations.

Current therapy is presented for each disorder and supplemented with a separate section on clinical pharmacology that describes general principles, new ad-

vances (eg, the role of drug receptors, plasma concentration monitoring), details of pharmacologic groups and specific agents, and even a discussion on the use of placebos. The use of complex equipment (eg, respirators) is also described. Prophylaxis is emphasized wherever possible. Finally, reference guides are provided for checking normal values, calculating dosages, and converting weights, measures, and volumes to metric equivalents.

Can so many subjects be covered adequately in a single book? You, the reader, must make the ultimate judgment, but we believe the answer is in the affirmative. This edition required a concerted effort by many people, beginning with an internal analysis and critique of the previous edition, even though it enjoyed highly favorable reviews and outstanding reader acceptance. Sections of that book were then sent to outside experts, who had had nothing to do with its preparation, to solicit their most candid criticism. Published reviews and letters received from readers were analyzed. Next, the Editorial Board met to compare reviews and critiques and to plan this 15th Edition. Distinguished special consultants were enlisted to provide additional expertise. Then, 269 authors with outstanding qualifications, experience, and knowledge were engaged. Their manuscripts were edited repeatedly in-house to retain every valuable morsel of knowledge while eliminating sometimes elegant, but unneeded, words. Each manuscript was then reviewed by a member of the Editorial Board or a consultant. In many cases, additional special reviewers were invited to comment. Every mention of a drug and its dosage was reviewed by a separate outside consultant. The objectives of all these reviews were to ensure adequate and relevant coverage of each subject, accuracy, and simple and clean exposition. The authors then reworked, modified, and polished their manuscripts. Almost all of the manuscripts were revised at least 6 times; 15 to 20 revisions were not uncommon. We believe that no other medical text undergoes as many reviews and revisions as THE MERCK MANUAL.

Owing to the extensive subject matter covered and a successful tradition, the style and organization of THE MANUAL have some unique characteristics. Readers are urged to spend a few minutes reviewing the Guide for Readers (p. viii), the Table of Contents *at the beginning of each section,* and the Index (p. 2577). Scrutiny of the arrangement of subject headings within each section, of internal headings within a subject discussion, and of boldfaced terms in the text will reveal a pattern of outlining intended to aid study of the text.

The foregoing is a simplified review of the complex, arduous, and rewarding 5-year enterprise that culminates in the presentation of this 15th Edition of THE MERCK MANUAL. The members of the Editorial Board, special consultants, contributing authors, and in-house editorial staff and their affiliations are listed on the pages that follow. They deserve a degree of gratitude that cannot be adequately expressed here, but we know they will feel sufficiently rewarded if their efforts serve your needs.

We hope this edition of THE MERCK MANUAL will be a welcome aid to you, our readers—compatible with your needs and worthy of frequent use. Suggestions for improvements will be warmly welcomed and carefully considered.

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Hydrazine sulfate may play a role in decreasing the anorexia associated with cancer; however, further testing is required.

Interferons (biologic-response modifiers): *Biologic proteins synthesized by leukocytes when invaded by viruses.* These proteins play important roles in the immune response. Interferons may be subclassified as α (leukocyte) interferon, β (fibroblast) interferon, and γ (lymphocyte) interferon. Their roles are under investigation; however, activity has been observed in therapy of breast cancer, myeloma, the non-Hodgkin's lymphomas, hairy cell leukemia, and renal cell carcinoma. **Toxicities** include nausea, alopecia, leukopenia, chills, fever, and myalgias.

§10. MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS

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mophytes and diffuse paraspinal ligamentous calcification, the usual textbook illustration, is *not* useful for early diagnosis. These advanced changes occur in a minority of patients and take an average of 10 yr to develop.

Differential diagnosis: One of the most important disorders to be differentiated is a **herniated intervertebral disk.** This latter condition is limited to the spine and has no systemic manifestations such as fatigue, anorexia, or weight loss; all laboratory tests, including the ESR, are normal. The only confirmation of a herniated disk is by myelography or CT scan.

The **DISH syndrome** (diffuse idiopathic skeletal hyperostosis) is a more difficult differential diagnosis. It occurs primarily in men > 50 yr and may resemble AS clinically and on x-ray. Patients may have spinal pain, stiffness, and insidious loss of spine motion. X-ray findings include ligamentous calcification most often affecting the cervical and lower thoracic spine. However, the sacroiliac and spinal apophyseal joints are not involved; the ESR is normal; and there is no link to HLA-B27.

Treatment

The patient's joint discomfort must first be relieved with antirheumatic drugs; long-range planning then begins—to prevent, delay, or correct deformity. To promote proper posture and joint motion, daily exercises and other supportive measures (eg, postural training or therapeutic exercise) are vital. The objective is to build up muscle groups that oppose the direction of potential deformities; ie, to strengthen extensor rather than flexor muscle groups. Long-range planning also must include the psychosocial and rehabilitative needs of the patient.

Nonsteroidal anti-inflammatory drugs (NSAIDs) facilitate exercise and other supportive measures by suppressing articular inflammation, pain, and spasm. The drugs listed in TABLE 108–2 should be considered first, since these are of proven value in AS. While aspirin or other salicylates may be tried first, they are seldom adequate and in no way comparable to the effectiveness of the other NSAIDs in the table. Tolerance or potential toxic risks rather than marginal differences in efficacy dictate drug choice. Patients should be monitored and warned of potential adverse reactions (see the NSAID discussion in RHEUMATOID ARTHRITIS, above). Patients receiving phenylbutazone or oxyphenbutazone should be routinely screened for rare but serious renal or hematopoietic

TABLE 108–2. DRUG THERAPY* OF ANKYLOSING SPONDYLITIS (AS)

Drug	Daily Dosage	
	Average	Range
Salicylates	4 gm	3–6 gm
Phenylbutazone†	300 mg	100–400 mg
and		
Oxyphenbutazone†	300 mg	100–400 mg
Indomethacin‡	100 mg	25–200 mg
Naproxen	750 mg	250–1000 mg
Sulindac	300 mg	100–400 mg

* The only nonsteroidal anti-inflammatory drugs with FDA approval for AS in the USA.

† Currently recommended only after other drugs have been tried first. Oxyphenbutazone is still available while supplies last, but manufacturing of the drug was stopped in the USA in mid 1985.

‡ Also available as a sustained-release preparation of 75 mg; the range of daily dosage is 75 to 150 mg.

(Modified from "Sustained-Release Indomethacin in the Management of Ankylosing Spondylitis" by J. J. Calabro, p. 44, in *The American Journal of Medicine*, Vol. 79(4c), October 25, 1985. Used with permission.)

adverse reactions, including fatal aplastic anemia; ie, complete blood and platelet counts as well as a urinalysis must be performed weekly for the initial 2 mo and monthly thereafter. The daily dose of NSAIDs should be as low as possible. However, complete drug withdrawal should be attempted only slowly and after all systemic and articular signs of active disease have been suppressed for several months.

Corticosteroids have limited therapeutic value, and their long-term use is associated with many serious adverse effects (see also Ch. 283). For acute iritis, topical corticosteroids (and mydriatics) usually are adequate; oral corticosteroids are rarely indicated. Intra-articular corticosteroids may be beneficial, particularly when 1 or 2 peripheral joints are more severely inflamed than others, compromising exercise and rehabilitation.

Radiotherapy to the spine, while an effective form of therapy, is recommended only as a last resort; the risk of subsequently developing acute myelogenous leukemia is tenfold. The **slow-acting (remittive) drugs** used in RA, such as IM gold, are not effective for AS. **Narcotics,** strict analgesics, and muscle relaxants should be prescribed only for short periods to control severe back pain and spasm, since they lack anti-inflammatory properties.

SJÖGREN'S SYNDROME (SS)

A chronic, systemic inflammatory disorder of unknown etiology, characterized by dryness of the mouth, eyes, and other mucous membranes and often associated with rheumatic disorders sharing certain autoimmune features (eg, RA, scleroderma, and SLE) and in which lymphocyte infiltration into affected tissues is seen. An association has been found between HLA-DR3 antigen and **primary SS** (*without associated connective tissue disease*—see below). The syndrome is more common than SLE but less common than RA.

Pathophysiology, Symptoms, and Signs

In some, SS affects only the eyes or mouth **(primary SS; sicca complex; sicca syndrome);** in others, there is an associated generalized collagen vascular disease **(secondary SS).**

Ocular symptoms occur when atrophy of the secretory epithelium of the lacrimal glands causes desiccation of the cornea and conjunctiva **(keratoconjunctivitis sicca,** discussed in Ch. 219). In advanced cases, the cornea is severely damaged and epithelial strands hang from the corneal surface **(keratitis filiformis).**

One third of SS patients develop **enlarged parotid glands** that are usually firm, smooth, fluctuating in size, and mildly tender. Chronic salivary gland enlargement is rarely painful. Intraductal cellular proliferation in the parotid gland causes luminal narrowing and eventual formation of compact cellular structures termed epimyoepithelial islands. When salivary glands atrophy, saliva diminishes, and the resulting extreme dryness of the mouth and lips **(xerostomia)** inhibits chewing and swallowing and promotes tooth decay and calculi formation in the salivary ducts. Taste and smell faculties may be lost.

Desiccation may also develop in the skin and in mucous membranes of the nose, throat, larynx, bronchi, vulva, and vagina. Alopecia may occur. Dryness of the respiratory tract often leads to lung infections and sometimes to fatal pneumonia.

Other manifestations: GI effects are associated with mucosal or submucosal atrophy and diffuse infiltration by plasma cells and lymphocytes. Chronic hepatobiliary disease is often associated with SS, as is pancreatitis (exocrine pancreatic tissue is similar to that of salivary glands). Fibrinous pericarditis is the commonest cardiovascular feature. Sensory neuropathy is common, especially of the 2nd and 3rd divisions of the 5th cranial nerve. Approximately 20% of SS patients have renal tubular acidosis; in many, renal concentrating ability is decreased. Interstitial nephritis is frequent; glomerulone-

phritis unusual. Patients with parotid enlargement, splenomegaly, and lymphadenopathy may develop pseudolymphoma or malignant lymphoma. The incidence of lymphoma is increased 44-fold for SS patients, who are also at increased risk for Waldenström's macroglobulinemia.

Diagnosis and Prognosis

One suspects SS with dryness of the eyes and mouth; joint inflammation completes the classic triad. Arthritis occurs in about 33% of patients and is similar in distribution to that seen in RA; however, joint symptoms in SS tend to be milder and rarely lead to destruction. Some patients with undiagnosed SS who have rheumatic symptoms may not complain spontaneously of sicca complex; SS is then defined by laboratory evaluation.

When bilateral parotid enlargement occurs in conditions such as hyperlipoproteinemia, malnutrition, cirrhosis, or diabetes mellitus, the glands are soft and puffy, in contrast to the firm glands of SS; oral dryness is absent.

Diagnostic procedures and laboratory findings: The **Schirmer test** measures the quantity of tears secreted in 5 min in response to irritation from a filter paper strip placed under a lower eyelid. A young person normally moistens 15 mm of the paper strip. Since hypolacrimation occurs with aging, 33% of normal elderly persons may wet only 10 mm in 5 min. Most persons with SS moisten < 5 mm/5 min, although about 15% of test results are false-positive and 15% false-negative. **Ocular staining** with a drop of **rose bengal solution** into the eye is highly specific. In SS, the portion of the eye filling the palpebral aperture takes up the dye, and red triangles with their bases toward the limbus are seen. **Tear breakup time, tear lysozyme concentration,** and **slit-lamp examination** are also useful.

Salivary glands are evaluated by **salivary flow, sialography,** and **salivary scintiscan. Biopsy** of the readily accessible labial salivary glands confirms the diagnosis when foci of lymphocytes and plasma cells associated with atrophy of acinar tissue are seen.

Remarkable immunologic reactivity, detected in blood serum, is characteristic of SS; most patients have elevated levels of antibodies against γ-globulin, nuclear protein, and many tissue constituents. Precipitating antibodies to nuclear antigens (identified by immunodiffusion analysis), termed SS-B antibodies, are highly specific for primary SS. Rheumatoid factor is present in > 70% of cases; the LE cell preparation is positive in 15 to 20%. The VDRL test is negative. ESR is elevated in 70% of patients. One third of patients have anemia; ¼, leukopenia and eosinophilia. Urinalysis may show proteinuria, reflecting interstitial nephritis.

Prognosis in SS is often related to the associated connective tissue disorder, although death may also result from pulmonary infection and, rarely, renal failure or lymphoma.

Treatment

For care of **ocular symptoms** see KERATOCONJUNCTIVITIS SICCA in Ch. 219.

Oral complications: Dryness that promotes ductal calculi and rampant dental caries may be avoided by sipping fluids throughout the day, chewing sugarless gum, and using a 2% solution of methylcellulose as a mouthwash. Drugs that decrease salivary secretion, such as decongestants and antihistamines, should be avoided. Fastidious oral hygiene and regular dental supervision are essential. Calculi must be promptly removed, preserving viable salivary tissue. The temporary pain of suddenly enlarged salivary glands is best treated only with analgesics.

Connective tissue involvement usually is mild and chronic; therefore, corticosteroids and immunosuppressive agents are indicated only occasionally, eg, in a patient with severe vasculitis or visceral involvement. Irradiation and drugs that increase the risk of lymphoproliferative disorders and infections should be avoided.

LYME DISEASE

(LD; Lyme Arthritis)

A tick-transmitted, spirochetal, inflammatory disorder best recognized clinically by an early skin lesion, erythema chronicum migrans ***(ECM)****, that may be followed weeks to months later by neurologic, cardiac, or joint abnormalities.*

Etiology, Epidemiology, and Pathophysiology

The illness is caused by a newly discovered spirochete, *Borrelia burgdorferi*, transmitted by the minute tick *Ixodes dammini* and related ticks. The disease was recognized in 1975 because of close geographic clustering of cases in the small community of Lyme, Connecticut. It has since appeared in over half the states in the USA, especially in foci along the northeastern coast from Massachusetts to Maryland, in Wisconsin, and in California and Oregon. It also has appeared abroad. Onset usually is in the summer and early fall and occurs at any age and in either sex, although most patients are children and young adults living in heavily wooded areas. LD is now the most commonly reported tickborne illness in the USA.

B. burgdorferi has been cultured from the blood, skin (ECM), and spinal fluid of LD patients. The spirochete enters skin at the site of a tick bite. After an incubation period of 3 to 32 days, the organism migrates outward in the skin (ECM), is spread in lymph (regional adenopathy), or is disseminated in blood to organs or other skin sites. The spirochete has been seen in secondary skin lesions, and in inflamed synovia.

LD is associated with characteristic immune findings. Over 85% of patients with subsequent arthritis have, in the prearticular (ECM) phase, serum cryoglobulins containing IgM (reflecting high serum IgM levels), compared to < 15% of patients without subsequent arthritis. Besides having prognostic value, these differences may represent different ways of responding to an immune stimulus, and may be determined genetically. In preliminary studies, patients have an increased frequency of the B cell alloantigen HLA-DR2 but not of HLA-B27 (as in the spondyloarthropathies).

More direct evidence for circulating immune complexes (eg, abnormal C1q-binding activity) is found in sera of most patients with ECM. These complexes tend to persist in the circulation of patients who develop neurologic or cardiac abnormalities. By the time arthritis appears, immune complexes are no longer evident in most sera but are found systematically in synovial fluid, and in higher titer than in concomitant sera.

Synovial membrane from affected joints may be indistinguishable from that of RA (see above). Nonspecific findings include villous hypertrophy, vascular congestion, and colonization with lymphocytes and plasma cells that may resemble early lymphoid follicles and, as in RA, are presumably capable of producing antibody locally. In addition, there may be an obliterative endarteritis and (rarely) demonstrable spirochetes. Pannus formation and erosion of cartilage and bone may occur.

The histology of ECM resembles that of an insect bite—epidermal and dermal involvement at the center (which is often indurated), dermal in the periphery. All layers of the epidermis are heavily infiltrated with mononuclear cells around blood vessels and skin appendages. At the center there is edema of the papillary dermis, and intra- and extracellular edema and a thickened keratin layer in the epidermis.

Symptoms, Signs, and Course

ECM begins as a red macule or papule, usually on the proximal portion of an extremity or on the trunk (especially the thigh, buttock, or axilla), that expands, often with central clearing, to a diameter as large as 50 cm. At least 75% of patients with Lyme disease have this early lesion. Of these individuals, about 25% report having been bitten at that site by a minute tick 3 to 32 days before onset of ECM. Soon after onset of ECM, nearly half the patients develop multiple, usually smaller, lesions without indurated centers. ECM generally lasts for a few weeks; evanescent lesions may